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Cough Due to Asthma and Nonasthmatic Eosinophilic Bronchitis

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Abstract Asthma and nonasthmatic eosinophilic bronchitis are among the most common causes of chronic cough, accounting for about 25 and 10% of cases, respectively. Chronic cough due to asthma may present in isolation in which case it is known as cough-variant asthma. Nonasthmatic eosinophilic bronchitis is characterized by the presence of eosinophilic airway inflammation in the absence of variable airflow obstruction or airway hyperresponsiveness. Both conditions share many immunopathological features with the exceptions to date of mast cell infiltration into the airway smooth muscle, increased IL-13 expression, and narrowing and thickening of the airway wall, which are features reserved to asthma. In most cases the trigger that causes the cough is uncertain. However, removal of potential triggers is important to consider, in particular with respect to occupational exposure to known sensitisers. In both conditions there is subjective and objective improvement following treatment with inhaled corticosteroids, which is associated with the presence of an airway eosinophilia. Whether eosinophilic inflammation is the cause of cough or an epiphenomenon is uncertain, but the failure of anti-IL-5 to modify cough in asthma has questioned a causal association. In asthma, β-agonist theophylline, leukotriene receptor antagonist, and oral corticosteroid therapy improve cough. In noneosinophilic bronchitis, some patients require oral corticosteroids but the benefit of other additional therapies is unknown. In general, response to therapy in both conditions is very good and the limited long-term data available suggest that both usually have a benign course, although in some cases persistent airflow obstruction may occur.

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Introduction

Chronic cough, defined as a cough lasting for more than 8 weeks with no overt clinical and radiological evidence of lung disease, is a common reason for referral to a specialist. Several series have shown that a cause of persistent cough can be identified relatively simply in 80–95% of cases by using an "anatomical diagnostic" protocol [1–6]. Asthma has consistently been reported as a major cause of chronic cough. The development of a noninvasive assessment of airway inflammation led in 1989 to the identification of a condition that manifests as a corticosteroid-responsive chronic cough in nonsmokers without the abnormalities of airway function that characterize asthma, but with a sputum eosinophilia [7]. This condition was described as nonasthmatic eosinophilic bronchitis. This review summarises our current understanding of the similarities and differences between asthma and nonasthmatic eosinophilic bronchitis in terms of the underlying immunopathogenesis, natural history, and clinical management. The main features and differences between nonasthmatic eosinophilic bronchitis, cough-variant asthma, and classic asthma are summarized in Table 1.

A Common Cause of Chronic Cough: Definition, Diagnosis, and Prevalence

Multiple prospective studies have shown that asthma is among the most common causes of chronic cough (24–29%) in adult nonsmokers [1–6]. Typically, cough is

Table 1 Clinical and pathological features of eosinophilic bronchitis compared with classic asthma and cough-variant asthma

	Eosinophilic bronchitis	Classic asthma	Cough-variant asthma
Symptoms	Cough, often associated with upper-airway symptoms	Dyspnea, cough, wheeze	Isolated cough
Atopy	Same as general population	Common	Common
Airway hyperresponsiveness	Absent	Present	Present
Cough reflex hypersensitivity	Increased	Normal	Normal or increased
Response to bronchodilator	Absent	Good	Good
Response to corticosteroids	Good	Good[a]	Good[a]
Sputum eosinophilia	Always	Usually	Usually
Bronchial biopsy eosinophilia	Very Common	Common	Common
Mast cells within airway smooth muscle bundles	No	Yes	Yes

[a] Good when a sputum eosinophilia is present

associated with the more usual symptoms of dyspnea and wheezing but may present in isolation in which case it is known as cough-variant asthma [8]. In a patient suspected of having asthma as the primary cause of chronic cough but in whom physical examination and spirometry findings are nondiagnostic, bronchial challenge testing, e.g., methacholine inhalation test, should be performed to confirm the presence of asthma. The diagnosis of asthma as the cause of cough is confirmed following resolution after antiasthma treatment.

Nonasthmatic eosinophilic bronchitis is defined as a chronic cough in patients with no symptoms or objective evidence of variable airflow obstruction, normal airway hyperresponsiveness (provocative concentration of methacholine producing a 20% decrease in FEV_1 [PC_{20}] > 16 mg/ml), and a sputum eosinophilia [1]. A greater than 3% nonsquamous cell sputum eosinophil count is used as an indication of eosinophilic bronchitis as this is outside the 90th percentile for normal patients (1.1%) [9] and this level of sputum eosinophilia has been associated with a corticosteroid response in COPD and asthma [10, 11]. Exhaled nitric oxide levels are usually higher in nonasthmatic eosinophilic bronchitis [12, 13], but its role in the diagnosis of nonasthmatic eosinophilic bronchitis has not been formally evaluated.

The prevalence of nonasthmatic eosinophilic bronchitis is uncertain as most reports of the causes of chronic cough have not included measures of airway inflammation. In a 2-year prospective study of chronic cough [1], where induced sputum was performed in all patients in whom the diagnosis remained unclear after simple clinical assessment and a methacholine inhalation test, 91 patients with chronic cough were identified among 856 referrals. A diagnosis leading to a successful treatment was reached in 85 (93%) of the cases. Nonasthmatic eosinophilic bronchitis using the above definition was identified in 12 (13.2%) patients, representing 30% of those who had a sputum induction. Studies in which assessment of airway inflammation has been undertaken in chronic cough patients have shown that nonasthmatic eosinophilic bronchitis accounts for 10–30% of cases referred for specialist investigation [1–3].

Pathogenesis: Similarities and Differences

The aetiology of asthma and nonasthmatic eosinophilic bronchitis is usually unknown, although both can be associated with exposure to an occupational sensitiser or to a common inhaled allergen [14]. These two conditions share many immunopathological features, including a similar degree of sputum [13, 15], bronchoalveolar lavage [13, 16] and biopsy eosinophilia, and a similar degree of basement membrane thickening [13, 17]. Similarly, asthma and nonasthmatic eosinophilic bronchitis are associated with increased sputum concentrations of important effector mediators cysteinyl-leukotrienes and eosinophilic cationic protein [15]. Interestingly, histamine and PGD_2 sputum concentrations are increased only in nonasthmatic eosinophilic bronchitis, suggesting that activation of mast cells in superficial airway structures is a particular feature of this condition and raises the possibility that localisation of activated mast cells might differ in asthma and nonasthmatic eosinophilic bronchitis. In support of this, mast cell numbers in bronchial brushings were increased in nonasthmatic eosinophilic bronchitis compared to asthma [16]. In asthma, mast cell numbers in airway smooth muscle were increased but not in nonasthmatic eosinophilic bronchitis [17], and the number of airway smooth muscle mast cells was inversely correlated with airway hyperresponsiveness [17, 18]. Interleukin-13 expression is increased in

asthma in bronchial submucosa, sputum, and peripheral blood T cells [19–22]. Although airway remodeling is a feature of both conditions, the consequent effect upon airway geometry is distinct, with airway narrowing observed only in asthma [23]. Thus, key factors determining the different functional association of airway inflammation in nonasthmatic eosinophilic bronchitis and asthma might be the microlocalisation of mast cells to the airway smooth muscle bundle, increased IL-13 expression, and airway narrowing resulting in airway hyperresponsiveness and variable airflow obstruction, and an epithelial infiltration producing bronchitis and cough.

Natural History

The natural history of nonasthmatic eosinophilic bronchitis has had limited study. A 10-year follow-up evaluation of 12 patients with nonasthmatic eosinophilic bronchitis suggests that that this condition is generally benign and self-limiting [24]. A larger series of patients recently reported suggests that this condition is rarely self-limiting [25]. Fifty-two patients from 1996 from 2003 were identified with nonasthmatic eosinophilic bronchitis and follow-up data of more than 1 year from 32 of these patients were available. Three (9%) patients developed asthma with typical symptoms and airway hyperresponsiveness. Twenty-one (66%) had persistent symptoms and/or ongoing airway inflammation. Only one patient with nonasthmatic eosinophilic bronchitis had complete resolution of symptoms and had no sputum eosinophilia while not on corticosteroid therapy. Five (16%) developed fixed airflow obstruction, although the decline in FEV_1 in the whole group of patients with nonasthmatic eosinophilic bronchitis was not greater than in normal controls.

A case has been reported of a patient who over a 2-year period developed persistent airflow obstruction [26]. The patient's cough improved with inhaled corticosteroids but the sputum eosinophilia continued. Several studies have observed that 30–40% of patients with COPD without a history of asthma and with no bronchodilator reversibility have sputum evidence of an airway eosinophilia [10, 27]. This observation provides one possible explanation for the presence of eosinophilic airway inflammation in some patients with COPD without apparent pre-existing asthma in that nonasthmatic eosinophilic bronchitis may in some circumstances lead to COPD.

Similarly, there is a paucity of data on the natural history of cough-variant asthma. In a 4-year retrospective study of 42 patients, 7 went into remission and 13 developed classic asthma [28]. Whether patients develop fixed airflow obstruction is uncertain.

Treatment

Anti-inflammatory treatment with inhaled corticosteroids and avoidance strategies when the inflammation is due to occupational exposure or inhaled allergen are the mainstay therapies for asthma and nonasthmatic eosinophilic bronchitis.

In asthma and cough-variant asthma the cough typically improves with inhaled corticosteroid therapy and bronchodilators (reviewed in [29]). Small trials of the theophyllines nedocromil and zafirlukast have also demonstrated some efficacy. Current recommendations are to use inhaled corticosteroids and bronchodilators as first-line therapy followed by leukotriene receptor antagonists and exceptionally to use systemic corticosteroid therapy. Measures of airway inflammation may be helpful in these refractory patients to guide the intensity of corticosteroid therapy as patients with chronic cough without evidence of eosinophilic inflammation do not respond to corticosteroids [30].

In nonasthmatic eosinophilic bronchitis, patients improve symptomatically and have a significant decrease in their sputum eosinophil count following inhaled corticosteroids [31, 32]. In one study [32], capsaicin cough sensitivity, which was moderately increased before treatment, improved toward normal after treatment with budesonide (400 μg inhaled twice daily) for 4 weeks, and there was a significant positive correlation between the treatment-induced change in cough sensitivity and sputum eosinophil count. These findings suggest that heightened cough sensitivity contributes to the cough in nonasthmatic eosinophilic bronchitis and that eosinophilic airway inflammation is causally associated with the increased cough sensitivity. However, importantly in a group of severe asthmatics, anti-IL-5 therapy had profound effects upon the frequency of severe exacerbations without an impact upon cough [33]. This questions a causal relationship between eosinophilic inflammation in asthma and cough and perhaps raises the potential importance of other mechanisms such as mast cell interactions with superficial nerves. Very occasionally oral corticosteroids are required to control symptoms and eosinophilic inflammation. The role of other potential therapeutic agents such as antihistamines and antileukotrienes needs to be investigated.

Conclusion

Asthma and nonasthmatic eosinophilic bronchitis are common, treatable causes of chronic cough. The airway inflammation is similar in both conditions but is associated with quite different abnormalities of airway function.

These differences might be related to the site of mast cell infiltration of the airways and airway narrowing in asthma. Future studies should look at the role of other noninvasive markers of airway inflammation in the chronic cough clinic, further define the natural history of these conditions, and investigate the effects of other therapies.

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